Association Between Troponin Levels and Visceral Infarction in Patients with Acute Ischemic Stroke

Shobana Ramasamy, BA,* Praneil Patel, MD,† Ajay Gupta, MD, MS,†
Peter M. Okin, MD,‡ Santosh Murthy, MD, MPH,* Babak B. Navi, MD, MS,*
Hooman Kamel, MD,* and Alexander E. Merkler, MD*

Background: Visceral infarctions appear to be more common in patients with embolic stroke subtypes, but their relation to troponin elevation remains uncertain. *Methods:* Among patients with acute ischemic stroke enrolled in the Cornell AcutE Stroke Academic Registry (CAESAR) from 2011 to 2016, we included those with troponin measured within 24 hours from stroke onset and a contrast-enhanced abdominal computed tomographic scan within 1 year of admission. A troponin elevation was defined as a value exceeding our laboratory's upper limit of normal (.04 ng/ mL) in the absence of a clinically recognized acute ST-segment elevation myocardial infarction. Visceral infarction was defined as a renal or splenic infarction as ascertained by a single radiologist blinded to patients' other characteristics. Multivariable logistic regression was used to evaluate the association between elevated troponin and visceral infarction. *Results:* Among 2116 patients registered in CAESAR from 2011 to 2016, 153 patients had both a troponin assay and a contrast-enhanced abdominal computed tomographic scan, of whom 33 (21%) had an elevated troponin and 22 (14%) had a visceral infarction. The prevalence of visceral infarction was higher among patients with an elevated troponin (30%; 95% confidence interval [CI], 16%-49%) than among patients without an elevated troponin (10%; 95% CI, 5%-17%) ($P = .003$). After adjustment for demographics and comorbidities, we found a significant association between elevated troponin and visceral infarction (odds ratio, 3.9; 95% CI, 1.5-10.4). *Conclusions:* Among patients with acute ischemic stroke, elevated troponin was associated with visceral infarction. Our results demonstrate that poststroke troponin elevation may indicate the presence of underlying embolic sources.

Key Words: Stroke—troponin—ESUS—visceral infarction

From the *Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology; †Department of Radiology; and ‡Department of Medicine, Weill Cornell Medical College, New York, NY.

Received November 7, 2018; revision received July 15, 2019; accepted September 24, 2019.

Funding: Dr. Ajay Gupta acknowledges research support from the National Institutes of Health (KL2TR000458, R01NS092802, and R01NS105144). Dr. Murthy acknowledges research support from the National Institute of Neurological Disorders and Stroke (grant K23NS105948) and the Leon Levy Foundation. Dr. Navi acknowledges research support from the National Institute of Neurological Disorders and Stroke (grant K23NS091395) and the Florence Gould Endowment for Discovery in Stroke. Dr. Kamel acknowledges research support from the National Institute of Neurological Disorders and Stroke (grants K23NS082367, R01NS097443, and U01NS095869) and the Michael Goldberg Research Fund, serving as a steering committee member of Medtronic's Stroke AF trial, serving on an advisory board for Roivant Sciences. Dr. Merkler acknowledges research support from the National Institutes of Health/National Center for Advancing Translational Science (grant KL2TR002385), the American Heart Association (grant 18CDA34110419), and the Leon Levy Foundation.

Address correspondence to Alexander E. Merkler, MD, Department of Neurology, Weill Cornell Medicine, 525 East 68th Street, F610, New York, NY 10065. E-mail: alm9097@med.cornell.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104449

Visceral infarctions are frequently found in patients with acute ischemic stroke and are more common in patients with embolic stroke subtypes, suggesting a proximal embolic source.[1–5] In addition, many patients with acute ischemic stroke have elevations in cardiac troponin (cTn). Despite having neither typical symptoms nor signs of an acute coronary syndrome, up to one third of patients have elevations in cTn above the diagnostic threshold to suggest acute myocardial injury; when using high sensitivity assays, this rate can be as high as 60%.[6,7] Although elevations in cTn are frequently observed in patients with acute ischemic stroke, their etiology remains unclear. In the absence of an acute coronary syndrome, elevations in cTn may be due to chronic kidney disease, congestive heart failure, respiratory disease, neurogenic stunned myocardium, or insular injury; however, other emerging data suggest that elevations in cTn may also reflect an underlying cardioembolic source.[8–13] We therefore evaluated whether elevations in cTn are associated with the presence of visceral infarction among patients with acute ischemic stroke. We hypothesized that there would be an association between elevated cTn and visceral infarction since these may reflect a shared cardioembolic source.

Methods

Design and Population

We performed a retrospective cohort study using the Cornell Acute Stroke Academic Registry (CAESAR). All patients with stroke at NewYork-Presbyterian Hospital/ Weill Cornell Medical Center are prospectively enrolled into the American Heart Association's Get With The Guidelines—Stroke registry. Trained hospital analysts electronically entered into the Get With The Guidelines database information on patients' demographics, vascular risk factors, time and data of stroke onset, vital signs on admission, National Institutes of Health Stroke Scale score on admission, date of discharge, and ambulatory status at discharge. This registry provides the foundation for CAESAR, which is then supplemented through retrospective collection of additional clinical, laboratory, and radiographic data, including stroke subtype. Stroke subtype was retrospectively ascertained by a panel of neurovascular neurologists. We used the Trial of ORG 10172 in Acute Stroke Treatment classification and consensus embolic stroke of undetermined source (ESUS) definition to adjudicate the etiology of all srokes.[14,15] The vast majority of patients underwent a complete stroke evaluation, defined as at least 24 hours of telemetry, an echocardiogram, a head CT or brain MRI, and vascular imaging of the head and neck; this work-up was required for a diagnosis of ESUS. For this analysis, we included all adults (≥ 18 years of age) with acute ischemic stroke between 2011 and 2016 who had a contrast-enhanced abdominal computed tomographic (CT) scan within 1 year of stroke and who had a cTn drawn within 24 hours of stroke onset. The data and analytic methods of this study are available from the corresponding author upon reasonable request. The Weill Cornell Medicine institutional review board approved this study and waived the requirement for informed consent.

Measurements

Our predictor variable was a cTn elevation, defined in accordance with the fourth universal definition of myocardial infarction (MI) as a cTn level value above the 99th percentile of our laboratory's upper limit of normal (.04 ng/ mL) in the absence of a clinically recognized acute ST-segment elevation MI.[16,17] All cTn values were based on the cTnI assay. We excluded all patients without a cTn value within 24 hours of stroke onset. A clinically recognized acute ST-segment elevation MI was defined based on documentation in the medical record by the primary neurology attending, cardiology attending, or the hospitalization diagnosis list. An attending cardiologist interpreted all ECGs.

Our outcome of interest was visceral infarction, defined as either renal or splenic infarction determined from contrast-enhanced CT of the abdomen and pelvis and ascertained by a single radiologist blinded to patients' other characteristics including stroke subtype and cTn levels (Fig 1). We chose to limit our outcome to renal or splenic infarction due to their characteristic appearance on CT imaging.[18,19] If multiple abdominal CT scans were eligible for evaluation, the study closest in time to the date of stroke was evaluated. Since splenic pathology is difficult characterize definitively in the arterial phase, only CT exams with a portal venous phase were used for splenic evaluation. Thus, when multiple CT images were eligible in this context, a more remote study with a portal venous phase was used if necessary for splenic assessment.

As previously described,[5] the radiologist graded visceral infarctions as absent or possible or probable. Our inclusion definition of visceral infarction comprised possible and probable infarcts to maximize sensitivity. Probable infarcts required single or multiple regions of peripheral wedge-shaped hypoattenuation with the apex directed toward the hilum. An enhancing cortical rim was used to distinguish infarction from pyelonephritis if present. Possible infarctions involved an imaging appearance compatible with, but less specific for an infarction. Placement in this category was on the basis of a nonspecific morphology with less well-defined or more rounded region(s) of peripheral hypoattenuation. If available, ultrasound was reviewed to assess for a cystic lesion at the location of possible infarction. For the purposes of this analysis, both possible and probable infarctions were counted as visceral infarctions.

Covariates

To account for confounding factors that may explain differences in the association between elevations in cTn and visceral infarction, we used prospectively collected information on demographics and cardiovascular risk factors including: age, sex, race, insurance status, tobacco use, diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, atrial fibrillation, peripheral vascular disease, alcohol/drug abuse, and history of prior stroke.

Statistical Analysis

We used standard descriptive statistics with exact confidence intervals [CI] to evaluate patient characteristics. The t test or rank-sum test were used for continuous variables and the chi-square or Fisher's exact test for categorical variables. Multivariable logistic regression was used to examine the association between cTn elevation and visceral infarction after adjustment for age and the total number of vascular risk factors. In a sensitivity analysis, we additionally adjusted for history of solid or liquid malignancy and use of antithrombotic (antiplatelet or anticoagulant) medication at the time of hospital admission for stroke. In a subgroup analysis, we restricted our multivariable analysis to patients with ESUS or cardioembolic stroke subtypes. All statistical analyses were performed by S.L.R. and A.E.M. using Stata/MP (version 15, College Station, TX). The threshold of statistical significance was set at $\alpha = .05$.

Results

Among 2116 patients with acute ischemic stroke registered in CAESAR from 2011 to 2016, we identified 264 patients who underwent an abdominal CT scan within 1 year of admission for stroke. Of these patients, 153 patients had a cTn drawn within 24 hours of stroke and were included in our final cohort. The most common indications for abdominal CT scan were for evaluation of abdominal pain and to rule out malignancy. The median time delay between abdominal CT and stroke was 26 days (interquartile range, 12-105).

Among these 153 patients, 33 (21%) had an elevated cTn and 22 (14%) had at least 1 visceral infarction. The median cTn was .02 (interquartile range, 0-.04). Patients with an elevated cTn were more likely women, but otherwise had similar demographics and vascular risk factors compared to patients without a cTn elevation (Table 1). Patients with visceral infarctions were more likely to have atrial fibrillation but otherwise had similar demographics and vascular risk factors as compared to patients without visceral infarctions (Table 2).

The prevalence of visceral infarction was higher among patients with an elevated cTn (30%; 95% CI, 16%-49%) than among patients without an elevated cTn (10%; 95% CI, 5%-17%, $P = .003$). In the unadjusted model, there was an association between cTn elevation and visceral infarction (odds ratio [OR], 3.9; 95% CI, 1.5-10.1, $P = .005$). After adjustment for age and the total number of vascular risk factors, we found a significant association between elevated cTn and visceral infarction (OR, 3.9; 95% CI, 1.5-10.4, $P = .005$). Our results were unchanged in a sensitivity analysis in which we additionally adjusted our model for history of solid or liquid malignancy and use of antithrombotic medication (OR, 4.5; 95% CI, 1.6-12.4, $P = .004$) (Table 3).

In our subgroup analysis isolated to patients with ESUS or cardioembolic stroke (n = 111), we found a similar association between elevated cTn and visceral infarction (OR, 4.0; 95% CI, 1.2-13.6, $P = .03$).

Discussion

Among patients with acute ischemic stroke, an elevated cTn was associated with visceral infarction. These findings were unchanged when restricted to a subgroup of stroke patients with ESUS or cardioembolic stroke. This association supports the hypothesis that elevations in cTn suggest an underlying cardioembolic source.

Elevations in cTn frequently occur in patients with acute ischemic stroke,[6,7] although their underlying mechanism is uncertain. cTn is highly specific for myocardial injury[20] and among patients with acute ischemic stroke, elevations

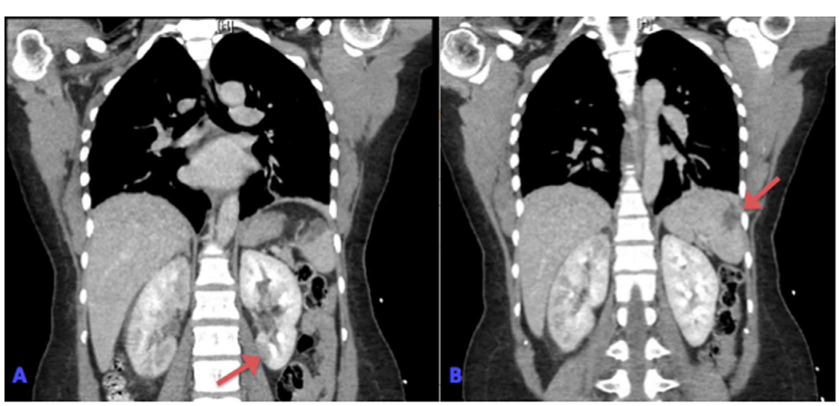

Figure 1. *Representative renal and splenic infarcts. (A) Renal infarct in coronal view (arrow). (B) Splenic infarct in coronal view (arrow).*

Table 1. *Characteristics of patients stratified by presence of elevated cardiac troponin*

Characteristic*	Elevated cardiac troponin (N = 33)	Normal cardiac troponin (N = 120)	*P* value
Age, mean (SD), y	72.7 (13.5)	68.1 (16.1)	.1
Female	24 (72.7)	58 (48.3)	.01
Race			.1
White	30 (90.9)	99 (82.5)	
Black	0 (0)	15 (12.5)	
Other	3 (9.1)	6 (5.0)	
Stroke Subtype			.001
Large-artery atherosclerosis	2 (6.1)	24 (20)	
Cardioembolic	12 (36.4)	15 (12.5)	
Small vessel	0 (0)	13 (10.8)	
Other	0 (0)	3 (2.5)	
Cryptogenic	19 (57.6)	65 (54.2)	
Hypertension	22 (66.7)	83 (69.2)	.8
Diabetes mellitus	8 (24.2)	34 (28.3)	.6
Coronary artery disease	7 (21.2)	22 (18.3)	.7
Peripheral vascular disease	3 (9.1)	7 (5.8)	.5
Dyslipidemia	12 (36.4)	48 (40.0)	.7
Chronic kidney disease	1.0 (3.0)	3.0 (2.5)	1.0
Atrial fibrillation	6 (18.2)	9 (7.5)	.1
Prior Stroke	5 (15.2)	24 (20.0)	.5
Congestive heart failure	2 (6.1)	2 (1.7)	.2
Chronic obstructive pulmonary disease	2 (6.1)	2 (1.7)	.2
Anticoagulant use†	4 (12.1)	11 (9.2)	.7
Antiplatelet use†	8 (24.2)	46 (38.3)	.1
Malignancy	13 (39.4)	32 (26.7)	.2
Tobacco use	1 (3.0)	8 (6.7)	.7
Drug or Alcohol use	1 (3.0)	1 (.8)	.4

Abbreviation: SD, standard deviation.
*Data are presented as number (%) unless otherwise specified.
†Use at the time of stroke presentation.

in cTn are associated with an increased risk of mortality and poor functional outcome.[6,10,21,22] Prior studies have found that elevations in cTn are more common in patients with ESUS,[8,9] suggesting that myocardial injury is associated with embolism. We found a novel association between cTn elevation and visceral infarction. As the presence of visceral infarction suggests a proximal embolic source,[5] our study strengthens the argument for a potential biological association between cTn elevation and embolism.

There are a number of limitations in this study. First, there is a potential for selection bias as we included only patients who underwent CT of the abdomen and pelvis within 1 year of stroke as part of routine care and among whom cTn was tested within 24 hours of stroke. However, among this same cohort of patients, we have previously found that there was no difference in demographics or vascular comorbidities or distribution of stroke subtype among patients who did or did not undergo CT of the abdomen and pelvis.[5] Similarly, we have previously found that cTn measurements were equally missing from patients with ESUS and those with known noncardioembolic stroke mechanisms.[8] Second, as we included CT scans obtained within 1 year of stroke admission, it is possible that there may have been significant change in patients' health in the interim time period between stroke and CT, which may have affected the presence of visceral infarction. Third, we lacked data on the presence of insular infarction, which is associated with elevations in cTn.[13] Fourth, although CAESAR is a large registry at a tertiary care hospital, it is a single-center cohort and therefore the results of this study may not be generalizable to all patients with acute ischemic stroke. Fifth, as evidenced by the wide confidence intervals, our analysis may have been underpowered.

In summary, we found an association between elevated cTn and visceral infarction among patients with acute ischemic stroke. Our results support the hypothesis that poststroke cTn elevation indicates the presence of underlying cardioembolic source. Patients with acute ischemic stroke and elevations in cTn should undergo a thorough cardiovascular evaluation as they appear to be at an elevated risk for embolic phenomena.

Table 2. *Characteristics of patients stratified by presence of visceral infarction*

Characteristic*	Visceral infarction (N = 22)	No visceral infarction (N = 131)	*P* value
Age, mean (SD), y	69.7 (16.4)	68.9 (15.6)	.9
Female	13 (59.1)	69 (52.7)	.6
Race			.3
White	21 (95.5)	108 (82.4)	
Black	0 (0)	15 (11.5)	
Other	1 (4.6)	8 (6.1)	
Type of visceral infarction			
Renal only	14 (63.6)		
Splenic only	4 (18.2)		
Renal and splenic	4 (18.2)		
Stroke Subtype			.1
Large-artery atherosclerosis	1 (4.6)	25 (19.1)	
Cardioembolic	8 (36.4)	19 (14.5)	
Small vessel	0 (0)	13 (9.9)	
Other	0 (0)	3 (2.3)	
Cryptogenic	13 (59.1)	71 (54.2)	
Hypertension	15 (68.2)	90 (68.7)	1.0
Diabetes mellitus	4 (18.2)	38 (29.0)	.4
Coronary artery disease	4 (18.2)	25 (19.1)	1.0
Peripheral vascular disease	0 (0)	10 (7.6)	.4
Dyslipidemia	6 (27.3)	54 (41.2)	.2
Chronic kidney disease	0 (0)	4 (3.1)	1.0
Atrial fibrillation	5 (22.7)	10 (7.6)	.03
Prior Stroke	6 (27.3)	23 (17.6)	.3
Congestive heart failure	2 (9.1)	2 (1.5)	.1
COPD	1 (4.6)	3 (2.3)	.5
Anticoagulant use†	2 (9.1)	13 (9.9)	1.0
Antiplatelet use†	7 (31.8)	47 (35.9)	.7
Malignancy	5 (22.7)	40 (30.5)	.5
Tobacco use	1 (4.6)	8 (6.1)	1.0
Drug or alcohol use	1 (4.6)	1 (.8)	.3
Troponin, median (IQR)	.04 (.02-.1)	.02 (0-.04)	

Abbreviations: IQR, interquartile range; SD, standard deviation.
*Data are presented as number (%) unless otherwise specified.
†Use at the time of stroke presentation.

Table 3. *Logistic regression models evaluating the relationship between troponin elevation and visceral infarction*

	OR (95% CI)	*P* value
Unadjusted	3.9 (1.5-10.1)	.005
Primary analysis*	3.9 (1.5-10.4)	.005
Sensitivity analysis†	4.5 (1.6-1.24)	.004
Subgroup analysis‡	4.0 (1.2-13.6)	.03

Abbreviations: CI, confidence interval; ESUS, embolic stroke of undetermined source; OR, odds ratio.
*Adjusted for age and the total number of vascular risk factors.
†In which we further adjusted for history of solid or liquid malignancy and use of antithrombotic medications.
‡In which we limited our cohort to patients with embolic stroke of undetermined source and cardioembolic stroke subtypes (n = 111).

Disclosures

None.

Conflict of interest

None.

References

1. Bekwelem W, Connolly SJ, Halperin JL, et al. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. Circulation 2015;132:796-803.
2. Orgel R, Wojdyla D, Huberman D, et al. Noncentral nervous system systemic embolism in patients with atrial fibrillation: results from ROCKET AF (Rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). Circ Cardiovasc Qual Outcomes 2017;10:e003520.
3. Slaoui T, Klein IF, Guidoux C, et al. Prevalence of subdiaphragmatic visceral infarction in cardioembolic stroke. Neurology 2010;74:1030-1032.
4. Abboud H, Labreuche J, Gongora-Riverra F, et al. Prevalence and determinants of subdiaphragmatic visceral

infarction in patients with fatal stroke. Stroke 2007;38: 1442-1446.

5. Finn C, Hung P, Patel P, et al. Relationship between visceral infarction and ischemic stroke subtype. Stroke 2018;49:727-729.
6. Kerr G, Ray G, Wu O, et al. Elevated troponin after stroke: a systematic review. Cerebrovasc Dis. 2009;28:220-226.
7. Scheitz JF, Nolte CH, Laufs U, et al. Application and interpretation of high-sensitivity cardiac troponin assays in patients with acute ischemic stroke. Stroke 2015;46: 1132-1140.
8. Merkler AE, Gialdini G, Murthy SB, et al. Association between troponin levels and embolic stroke of undetermined source. J Am Heart Assoc. 2017;6. pii: e005905.
9. Yaghi S, Chang AD, Ricci BA, et al. Early elevated troponin levels after ischemic stroke suggests a cardioembolic source. Stroke 2018;49:121-126.
10. Scheitz JF, Mochmann HC, Erdur H, et al. Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: analyses from the TRELAS cohort. Int J Cardiol 2014;177:886-893.
11. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol. 2010;9:105-118.
12. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352:539-548.
13. Krause T, Werner K, Fiebach JB, et al. Stroke in right dorsal anterior insular cortex is related to myocardial injury. Ann Neurol. 2017;8:502-511.
14. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
15. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429-438.
16. Apple FS, Jesse RL, Newby LK, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Clin Chem. 2007;53:547-551.
17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33: 2551-2567.
18. Suzer O, Shirkhoda A, Jafri SZ, et al. CT features of renal infarction. Eur J Radiol. 2002;44:59-64.
19. Miller LA, Mirvis SE, Shanmuganathan K, et al. CT diagnosis of splenic infarction in blunt trauma: imaging features, clinical significance and complications. Clin Radiol. 2004;59:342-348.
20. Seliger SL, Hong SN, Christenson RH, et al. High-sensitive cardiac troponin T as an early biochemical signature for clinical and subclinical heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). Circulation 2017;135: 1494-1505.
21. James P, Ellis CJ, Whitlock RM, et al. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. BMJ 2000;320:1502-1504.
22. Faiz KW, Thommessen B, Einvik G, et al. Prognostic value of high-sensitivity cardiac troponin T in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23:241-248.